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Review Article

Using Managed Entry Agreements as an Effective Tool to Handle the Uncertainty in Health Technology Assessments

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1. Context

Access of innovative medicinal products remains ever-tortuous path due to affordability challenges (1), lengthy evidence generation process (2), and regulatory stringencies (3). As a result, significant delay in treatments are envisaged, sometimes even compromising the life of the patient. To avoid such negative consequences despite promising potential of the medicines and to provide value-based healthcare, manufacturers often consider entering into a formal agreement with third party payers for timely access of such products, known as managed entry agreements (MEA) (4). In other words, MEA is a formal document which facilitates market access to several key medicinal products despite the uncertainty of its financial or clinical impact. Given their purpose to reduce financial and outcomes related risk, they are also known as pharmaceutical risk-based sharing agreement (PRBSA). Popular nomenclature for PRBSA includes outcomes-based schemes, risk-sharing agreements, coverage with evidence development (CED), access with evidence development, patient access schemes (PASs), conditional licensing, and managed entry schemes (5).

Historically, in 1995, the Centers for Medicare and Medicaid Services (CMS) (then known as the Health Care Financing Administration (HCFA)) established the coverage for certain items furnished in Food and Drugs Administration (FDA)-approved Investigational Device Exemption (IDE) trials in the United States. National coverage determination (NCD) processes were formally implemented in compliance with statutory norms laid in clinical trial policy since 2005 seeking study participation for cochlear implants and fluorodeoxyglucose (FDG)-positron emission tomography (PET), which was followed by the guidance on CED paradigm related to NCD in 2006 (6). Differing from cohort-based orientation, the Italian payers pioneered individual performance-based agreements (IPBA) in 2006 as a part of a project named CRONOS for the reimbursement of acetylcholinesterase inhibitors in Alzheimer's disease. In 2010, the cancer drugs fund (CDF) was developed to ensure access to expensive cancer medications, which are not appraised, under appraisal, or appraised but not recommended by national institute of health and care excellence (NICE) in the United Kingdom (7, 8).

Despite previous rejections regarding reimbursement by the Scottish Medicines Consortium (SMC), NICE also eventually adopted market access agreement (MAA) for the first time for therapy with high treatment costs. In December 2015, NICE provided first MAA-driven access recommendation for elosulfase alfa (Vimizim) used to treat Morquio A syndrome, which was followed by another MAA scheme for ataluren (Translarna) in Duchenne muscular dystrophy in April 2016 (9). Thus, utility of MAAs as an access route for drugs for rare diseases with limited evidence and high treatment cost uncertainties became evident. Concurrently, European Medicines Agency (EMA) also implemented pilot with adaptive pathway mechanism for access to the new medicines between 2014 and 2016 (10).

Due to several gaps identified after its implementation, revisions were made in CDF standard operating procedures in 2016. This indicated the perpetual scope of improvement in MAA structure. Compounded by lack of streamlined health financing systems, poor appraisal framework resulting from insufficient subject matter expertise, and limited scope of implementation, MAA execution in low- and middle-income countries remains a great challenge (11). Thus, the present narrative review provides a bird-eye view on need of MEA, its salient fea-

tures, and a brief about its utility areas. It proposes a road map for low- and middle-income countries to adopt such adaptive access pathways for medicines and medical devices.

2. MEA: When Needed?

Not all the medicines or medical device requires MEA-driven market access. The manufacturer could adopt MEA access pathway depending on the need of value demonstration and market situation. For example, if there is a dire need for any medicinal product to treat any patient population, or if there is a strong commercial competition to bring the same medicinal product to the market, adaptive pathways like MEA could be considered (12, 13). Secondly, when a product has guaranteed value for long-term clinical benefit, MEA may help ensuring rapid access. From the demand perspective, two broader purposes for MEA execution could be the need for price reduction and the need for further research. The former aims to reduce the financial risk and the later aims to reduce the decision uncertainty.

2.1. Types of MEAs

Based on the underlying risk reduction objectives, there are two types of MEAs: (1) finance-based MEA; and (2) performance-based MEA. Another emerging type of MEA is known as service-based MEA.

Finance-based MEAs (also known as commercial agreements) concentrate solely on monetary benefit regardless of clinical outcomes or patient-centricity. This may include fixed pricing for medicines for a certain period, discounted pricing, price-volume agreement (volume caps), or annualized rebate per-manufacturer arrangement (14). The discount amount is confidential to other payers. Such MEAs do not require detailed analysis of clinical data on product/treatment performance (patient health outcomes) (14). The classic example of such MEAs could be rate contracts for medicines and medical devices, where the rate of any product is fixed regardless of its quantity sold. Except for providing quick-fix solutions with transient monetary benefits, such agreements have been reported to fail in providing long-term, viable market access solutions for new medicines due to price confidentiality issues. This not only disrupts priority-setting based on the sole criterion of incremental cost-effectiveness ratio (ICER), but also complicates the health technology assessments (HTA) submissions due to unknown price of comparator with confidential discount even with an availability of discount-adjusted ICER (15).

On the other end, performance-based MEAs are designed to share the risk related to treatment performance between payer and the manufacturer, substantiating their nomenclature as performance-based risk sharing agreements (PBRSA) (5). The treatment performance is evaluated using the health outcome data of any therapeutic intervention. For example, Bortezomib and Pomalidomide underwent through performance-based MEA where multiple myeloma patients not meeting the specific treatment criteria received rebate for these drugs in the UK and France, respectively. The underpinning strategy for such MEA is to pay against evidence from agreed clinical study or real-world data collection on the therapeutic effect of any intervention. The data collection phases for this kind of MEA are initiated following regulatory approval and are linked with post-launch coverage decisions. The uncertainties addressed by PBRSA-oriented data collection is expected to address uncertainties related to efficacy/effectiveness of investigational medicinal product (IMP) with standard of care, heterogeneous study population and efficacy/effectiveness implications, temporal effects on health outcomes, clinical decision making, and appropriateness of treatable population depending on their responsiveness. Such assessment could be done on cohort of the patients (CED) or even for an individual patient [payment for performance (P4P) or payment by research (PbR)]. Several limitations of these MEAs include subjective societal desirability of PBRSA depending on its value of information (VOI), costly affair in extended data collection, and lack of research-intensive efforts in the evaluation.

While finance-based and performance-based MEAs may provide both individual and target population level contexts, service-based MEAs solely focus on target population. These kinds of mechanisms include addressing issues related to limited cashflows to payers, allocation of education budget to healthcare providers for their patients, adherence incentives, etc. (8). For example, if a medical technology is new in the market and healthcare professionals are paid for the patient-education for that technology's use, it would be an example of service-based MEA. Being a new concept, it requires further studies to assess its impact on overall pricing and reimbursement landscape.

2.2. Determinants of MEA Scheme Choice

In initial phase, there was no analysis framework for determining which scheme to choose under MEA. However, NICE decision support unit (DSU) guidance document in 2016 for analyzing risk in HTA (16) proposed two dimensions: (1) Price adjustment in form of conditional price rebate or straight discounts; and (2) further evidence collection in form of various types of scientific studies and analyses of the data. The need for either or both of them could be determined using four components: (1) costs; (2) quality-adjusted life-year (QALY) (effect measure) for any health outcome; (3) decision uncertainty (probabilistic sensitivity analysis and cost effectiveness acceptability curve); and (4) value for information (16). The fourth component is the heart of the whole MEA scheme analysis as it provides information about scope of uncertainty risk change after implementing any MEA. In lay explanation, it is a mathematical model which determines the degree

of the reduction of two types of uncertainty risk; one associated with payer's choice and one inherently associated with the strategy for health technology recommendations to the third-party payer by the decision maker.

2.3. Common Elements for MEA

Although both MEA strategies – price reduction and recommended for research (RwR) – are presented separately for conceptual understanding and illustrative purposes, they may be used in combination for synergistic results. In addition, given the increasing importance on personalized medicine and patient journey mapping, care quality improvement strategy may be considered with its exclusive focus on target population (Figure 1).

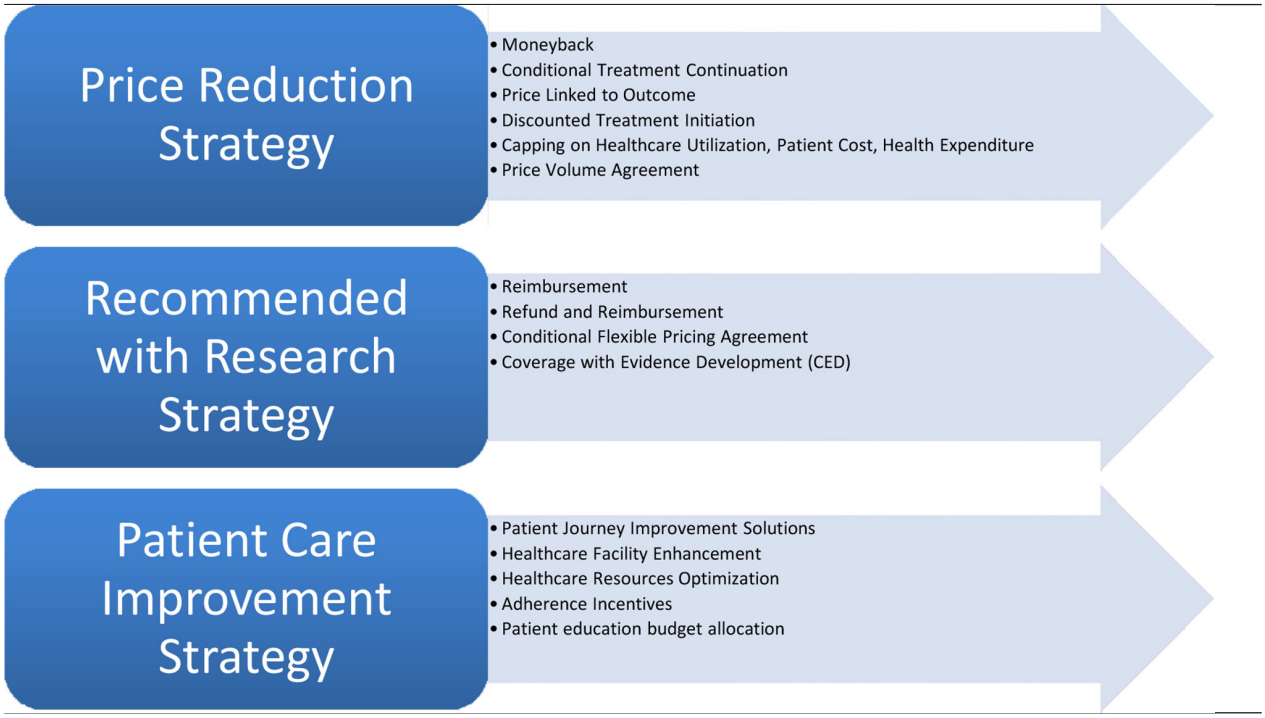

Figure 1. Various MEA strategies (adapted from NICE DSU guidance document and Dabbous et al., 2020) (8).

Deciding upon which of these strategies to adopt is the call to be taken by manufacturers. In some cases, HTA agencies may recommend the optimal MEA strategy to the drug manufacturer and expert clinician(s).

2.4. Considerations for MEA Applications

Unlike non-communicable diseases or infectious diseases, rare diseases possess challenges in terms of clinical research, resulting in poor quality of evidence and larger room for uncertainty. Furthermore, high prices of rare diseases treatment fail to ensure accessibility even after financial agreements. This could be attributed to huge budget impact associated with RDs, increasingly challenging price justification, and uneven access to RD therapies (17). There is high unmet clinical need for paediatric patients with rare diseases, thereby increasing pressure from parents and political lobby groups. This results in a compelling access requirement that remains to be fulfilled. Outcome based MEA (OB-MEA) is executed at individual or population level. The template of OB-MEA construct would be solely at the discretion of respective jurisdiction to which the patient would belong, thus causing outcome data sharing prohibitions. However, such prohibition blocks the establishment of robust evidence base that may inform to HTA body the need of reappraisal of RD therapy (18). Another discipline that uses MEAs for rapid access includes oncology solutions (19). Although basic theoretical information is available about the medical device MEAs, no substantial adoption of MEA approach in medical devices is noticeable till date. The possible reason could be the fluctuations in the observed outcomes due to their dependence on the user learning experience.

2.5. Challenges Associated with MEAs

Although it looks a promising pathway paving the way to accessing innovative medicines, it is not free from practical issues. Performance-based MEAs have not been optimally adopted due to confidential information. No public access is available for most of the MEAs executed between manufacturers and payers, rendering other stakeholders unaware about the actual agreement terms. This blocks the identification of potential scope of improvement or modification in the agreement design, resulting in un-

addressed discrepancies and thereby poor utilization of otherwise useful accessibility tool (20). That said, over-uptake of pharmaceutical product in absence of explicit definition of selection criteria for MEA implementation may also result from such fuzzy dynamics (21). Secondly, unlike drugs, value proposition in medical devices is not an easy task and requires a great pool of talent at both payers' and manufacturers' ends. Moreover, administrative limitation to work within siloed budgets compounded by lack of illustrative examples on how successfully value-based procurement strategies may work becomes a strong roadblock for exploring outcomes based MEA for medical devices (13, 22).

2.6. Low- and Middle-Income Countries and the Scope of MEAs

Low- and middle-income countries (LMICs) are yet to adopt MEA approach to benefit their population due to limited knowledge and poor health financing models (11). It has been warned that if LMICs continue to adopt volume-based healthcare development path, they would be at a risk of irreparable infrastructural gaps comprised of inconsistent data systems, as well as flawed health financing policies (23). To inculcate the urge for MEAs for innovative access to high-value therapies for LMIC target population, an interdisciplinary approach is recommended. The first and foremost requirement is of capacity building about pharmaco-economic modelling, including uncertainty analysis, effective value story development, and value-based pricing and reimbursement models (24). Another important consideration to enable MEA-driven access includes streamlining of third-party payment/reimbursement mechanism. In countries like India with majority of healthcare payment through out-of-pocket expenditure, such pay-for-performance concept is a mere theory. Ultimately, it would demand a strong political ground that would positively influence the pharma manufacturers to consider such payer-centric pricing models to achieve universal health coverage goals.

Nevertheless, authors believe that there are several touchpoints in the market access pathways, which, if approached differently, may help transform the existing volume-based pricing into value-based-pricing and reimbursement, especially in low resource settings. This includes: (1) needs assessment (where value enhancement is required?); (2) robust value assessment methods (how value is assessed and demonstrated?); (3) governance framework with an eye to value (who is the value chooser?); and (4) choice of outcome(s) (what is proposed as the value?). The last touchpoint is a crucial juncture as it determines the foundation of pricing and reimbursement decisions. Also, mixed views have been studied for several European countries in terms of involving "patients" as the stakeholders for OB-MEA for a few rare diseases in recent past (18). However, involvement of a physician with payer would connect the missing dots in while realistic identification of outcomes likely to be well responded by the patients and thereby worth paying for. Adopting similar practice within LMIC context would not only be foreseen to provide a boost to HTA adoption but also earlier access to innovative drugs and devices.

3. Conclusion

Uncertainty in HTA is a crucial concern and requires a tactful solution. Several developed countries have streamlined access pathway despite knowledge of HTA uncertainties through the MEAs. Although volume-based pricing solutions are the prevalent designs, outcome-based MEAs have gained interest of researchers and decision makers recently. For the effective implementation of MEA strategies in LMICs, a sound judgement call via a joint consensus between HTA agencies, payers, and manufacturers regarding the need for MEAs, a patient-centric political will and transparent evidence ecosystem are recommended.

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